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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/077,065 | 02/15/2002 | Venita I. DeAlmeida | P1872R1 | 3480 |

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| EXAMINER | |
|---|---|
| EWOLDT, GERALD R | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1644 | |

DATE MAILED: 12/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/077,065 | DEALMEIDA ET AL. | |
| | Examiner | Art Unit | |
| | G. R. Ewoldt, Ph.D. | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-52* is/are pending in the application.

4a) Of the above claim(s) *10-41 and 46-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 42-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed 9/27/06 in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's remarks, filed 9/27/06, have been entered.

2. Claims 10-41 and 46-52 stand withdrawn from further consideration by the examiner, 37 CFR 1.142(b).

Claims 1-9 and 42-45 are pending and under examination.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-9 and 42-45 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the specification provides insufficient evidence that the claimed method could be used to effectively treat insulin resistance or hypoinsulinemia, or be used to repair or regenerate muscle in a mammal.

As set forth previously,

The method of the instant claims presumably functions by employing an antagonist of Dkk-1, such as an antibody, such that Dkk-1 is unavailable for the downregulation of Wnt family proteins. Thus, it is actually the upregulation (or lack of downregulation) of Wnt proteins that would provide the treatment of insulin resistance or hypoinsulinemia, or the repair or regeneration of muscle. The specification implies that Wnt proteins activate numerous other proteins involved in the insulin-signaling cascade or the differentiation of myocytes into adipocytes. Presumably, upregulating Wnt proteins would upregulate downstream effectors leading to increased insulin metabolism and decreased differentiation of myocytes into adipocytes (which would presumably result in the repair or regeneration of muscle).

A review of the specification discloses just a single relevant example (Example 1) supporting the method of the instant claims. The example discloses that the culture of L6 myoblasts in a medium including Dkk-1 causes reduced insulin-stimulated glucose uptake, while the culture of 3T3/L1 fibroblasts in a medium including Dkk-1 causes increased insulin-stimulated glucose uptake and the decrease in the expression of some markers that would indicate adipocyte differentiation in said cells. The disclosure also teaches that the injection of Dkk-1 into mice causes altered expression of muscle specific genes and reduces insulin secretion, and that overexpression of *dkk-1* in transgenic mice causes reduced size and bodyweight in the animals. It is unclear how this disclosure is intended to enable the method of the instant claims.

The specification fails to disclose that, like many developmental genes, Wnt family genes are both developmental genes and proto-oncogenes (see for example, Behrens et al. 2004). As taught by LeFloch et al. (2005), "Inappropriate expression of Wnt/APC/β-catenin signaling pathways plays a critical role at the early stages in a variety of human cancers". Uematsu et al. (2003) "identified Wnt signaling in thoracic malignancies", including mesothelioma and non small cell lung cancer. Chen et al. (2003) links Wnt signaling to melanoma progression. Miyoshi et al. (2002) teaches that Wnt expression induces mammary tumors.

Regarding Dkk-1 in particular, Wang et al. (2000) show that p53 exhibits its tumor suppressor activity through Dkk-1-mediated downregulation of the Wnt signaling pathway. In a mesothelioma model, Lee et al. (2004) show that Dkk-1 exerts a tumor suppressive effect by antagonizing Wnt signaling. Finally, Gonzalez-Sancho et al. (2005) teach, "Our data indicate that the Wnt/β-catenin pathway is regulated by the induction of DKK-1 expression, a mechanism that is lost in colon cancer".

Clearly then, these combined teachings would not lead one of skill in the art to conclude that the downregulation of Dkk-1, causing the upregulation of Wnt, would be a good idea. While the specification provides some inconclusive teachings regarding the efficacy of a Dkk-1 antagonist for the treatment of insulin resistance or hypoinsulinemia, or the repair or regeneration of muscle, the prior art clearly teaches that the downregulation of Dkk-1, causing the upregulation of Wnt, would exacerbate, if not actually induce, any number of cancers - conditions far worse than the conditions the claimed method is intended to treat. Accordingly, it is the Examiner's position that the invention of the instant claims would require undue experimentation to practice as claimed.

Applicant's arguments, filed 9/27/06, have been fully considered but they are not persuasive. Applicant argues that Dkk-1 activity was "correlated" with the inhibition of Akt and cites several references in support of the claimed method. Applicant first cites Krook et al. (1997) and Krook et al. (1998).

A review of the references provides little support for the method of the instant claims. The Krook et al. references consider the effect of insulin sensitivity on Akt kinase activity in a mouse model. This is unrelated to the claimed method wherein Dkk-1 activity is asserted to have an effect on insulin sensitivity. A review of the references also reveals

that, even regarding Akt activity, "Little is known regarding the physiologically relevant downstream targets of Akt". Thus, the references demonstrate that so little is known about insulin resistance/sensitivity that an asserted effect on Akt activity cannot be considered to have risen to the level of invention.

Applicant cites Shao et al. (2000).

Again the authors studied the effect Akt activity in a mouse model. Again, this study is unrelated to the method of the instant claims. The authors begin to characterize the Akt signaling pathway, its involvement in GLUT4 translocation and glucose uptake, and draw conclusions such as, "we have shown that in the skeletal muscle and adipose tissue from db/db mice there is no difference in protein abundance and phosphorylation of Akt and p85α in the basal state. After insulin stimulation in *in vivo*, Akt-$Ser^{473}$ phosphorylation and tyrosine p85α phosphorylation are decreased…". One interesting conclusion was that, "Several lines of experimental evidence suggest that resistance to insulin-stimulated glucose transport may *not* be accompanied by resistance to insulin signaling at the mitogenic branches of insulin signaling". These finding again demonstrate that so little is known about insulin resistance/sensitivity that an asserted effect on Akt activity cannot be considered to have risen to the level of invention and they do not enable the method of the instant claims.

Applicant cites Strowski et al. (2004).

No article by Strowski et al. has been found in the application. It should be noted, however, that a 2004 reference would be unlikely to provide support for an invention with a priority date of 2001.

Applicant argues, "In the present case, the specification provides both *in vitro* and *in vivo* animal models demonstrating the ability of Dkk-1 to invoke the key features of insulin resistance, by impairing glucose tolerance *in vivo* and reducing uptake of glucose into muscle cells in vitro. The specification also demonstrates that Dkk-1 inhibits Akt, a key enzyme in the insulin signaling pathway, and whose deficient activity is considered by some studies as a marker of insulin resistance not only *in vitro*, but also in human NIDDM patients and an accepted animal model of insulin resistance".

As set forth above, it remains the Examiner's position that the disclosures of the instant specification do not adequately enable the methods of the instant claims.

Applicant cites Tuttle et al. (2001).

First note that Tuttle et al. (2001) is a post-filing references and thus, cannot be used to show the enablement of the claimed invention as of its priority date. Regardless, the reference again demonstrates that the method of the instant claims cannot be considered to have risen to the level of invention. For example, the reference teaches, "although the role of Aktl in cultured cell lines is well delineated, its physiological role in an intact organism has only recently begun to be addressed. Initial studies in *Drosophila melanogaster* not only demonstrated an essential developmental role for Akt, but also implicated a novel role of Aktl in the regulation of cell growth. Thus far, only studies in *Caenorhabditis elegans* have substantiated the role of Akt in the regulation of genes required for metabolisms. Because these studies focused on the role of Akt in invertebrate systems, *the orthologous role of Akt in higher life forms still remains to be established*" (emphasis added). Further, the reference teaches, "Our primary objective here was to elucidate the role of Aktl in the pancreatic β cell and evaluate its potential therapeutic prospects". This "objective" clearly indicates that the manipulation of Akt, much less Dkk-1 (as claimed) cannot be considered to be an invention even at the post-filing date of this reference's publication.

Applicant argues, "The Examiner argues there is evidence of record that questions the enablement of the claims citing a decreased glucose uptake in L6 muscle cells, but an increased glucose uptake in adipose cells. The Applicants respectfully disagree with the Examiner's assertion that the claimed methods are unpredictable, by disclosing that Dkk-1 exhibited differing results in differing tissue even in "simple" *in vitro* models.

Applicants emphasize, however, that the instant claims are not directed to the effects of Dkk-1 antagonists on a specific body tissue relative to other body tissues, but rather to the treatment of overall insulin resistance in a mammal. As discussed above, the specification is not limited to *in vitro* studies, but also discloses animal models that Dkk-1 impairs glucose tolerance and reduces insulin production in vivo in animal models".

Applicant's argument appears to be that, while the invention does not work in all of the Inventor's own simple *in vitro* model systems, it works *in vivo*. Said argument is not convincing given that the single *in vivo* model does not correlate in scope with the claimed invention.

Applicant cites Hallsten et al. (2002).

Applicant is again advised that post-filing references cannot establish that an invention was enabled as of its priority date. Regardless, the reference teaches nothing regarding the use of Dkk-1 antagonists.

Applicant again cites the single example of the specification wherein Dkk-1 was injected into experimental mice and a conclusion that said injection caused a decrease expression of certain muscle differentiation markers was drawn.

It is unclear to the Examiner how this experiment enables the claimed method. Effects of an excess of a protein do not necessarily relate to the effects of a reduced level of a protein.

Applicant argues that the present invention has not been shown to be unsafe and that a showing of complete safety is not required. Further, "undesirable side effects is not determinative in establishing a reasonable basis to question enablement upon safety grounds".

Applicant's argument may be true, however, the evidence provided by the Examiner clearly establishes the unpredictability of the claimed method. It remains the Examiner's position that in view of the references provided it is unclear and unpredictable just what might result form the manipulation of Dkk-1 *in vivo*. Further note that no rejection under 35 U.S.C. 101 has been made. Finally note that cancer is not generally considered to be simply an "undesirable side effect".

Applicant cites MPEP 2164.05(a) in arguing that "In general, the examiner should not use post-filing date references to demonstrate that the patent is non-enabling". However, the same section of the MPEP goes on to state, "If individuals of skill in the art state that a particular invention is not possible years after the filing date, that would be evidence

that the disclosed invention was not possible at the time of filing and should be considered. … an article published 5 years after the filing date of the application adequately supported the examiner's position that the physiological activity of certain viruses was sufficiently unpredictable so that a person skilled in the art would not have believed that the success with one virus and one animal could be extrapolated successfully to all viruses with all living organisms. Claims not directed to the specific virus and the specific animal were held nonenabled". In the instant case it is the Examiner's position that the post-filing art demonstrates the unpredictability of the claimed method and is thus, applicable.

Applicant specifically addresses Wang et al. (2000) arguing that the administration of Dkk-1 had no effect on the growth rate of two cancer cell lines and that the reference provides, "provides conflicting evidence concerning the effect of Dkk-1 on proliferation of cancerous cells, and is therefore insufficient to provide a reasonable basis to question the safety of the claims".

It would seem then that the reference provides further evidence of the unpredictability of manipulating Dkk-1. In this instance where cell proliferation would have been expected to have been seen, it was not. Clearly then, accurate predictions regarding the presence or absence of Dkk-1 cannot be made given the current limited knowledge of Dkk-1 activity and the pathways in which it is involved.

Applicant argues that the experiments of Uematsu et al. did not involve Dkk-1.

The experiments of the reference did establish that Wnt signaling is involved in certain malignancies. The Background of the instant specification establishes that Dkk-1 is involved in Wnt signaling.

Applicant argues that Chen et al. does not establish that Dkk-1 activity prevents carcinogenesis.

Chen et al. does establish that Wnt signaling is linked to melanoma progression.

Regarding Gonzales-Sancho et al., Applicant argues that, "the disclosed conflicting pattern of Dkk-1 overexpression and

underexpression seen among various cancers renders this reference ambiguous".

It would again seem that Applicant is arguing unpredictability. Still, the authors conclude, "Our data indicate that the Wnt/β-catenin pathway is regulated by the induction of DKK-1 expression, a mechanism that is lost in colon cancer".

Applicant argues that Lee et al. "does not provide any direct evidence, however, showing that Dkk-1 activity prevents carcinogenesis in healthy cells".

The reference teaches that Dkk-1 exerts a tumor suppressive effect by antagonizing Wnt signaling.

Applicant argues that Le Floch et al. "does not discuss Dkk-1 at all, and does not provide any direct evidence that Dkk-t activity prevents carcinogenesis".

The reference teaches that "Inappropriate expression of Wnt/APC/β-catenin signaling pathways plays a critical role at the early stages in a variety of human cancers". It has been established that Dkk-1 is involved in Wnt signaling.

Applicant argues that Miyoshi et al. "does not provide any direct evidence that Dkk-1 activity prevents carcinogenesis".

The reference teaches that Wnt expression induces mammary tumors. Again, it has been established that Dkk-1 is involved in Wnt signaling.

Applicant admits that Behrens et al. teaches "that Wnt signaling is a key pathway in cancer. Applicant argues, however, that the reference "does not provide any direct evidence, however, showing that Dkk-1 activity prevents carcinogenesis".

The fact that Wnt is a proto-oncogene and that Dkk-1 is involved in Wnt signaling provides evidence that the Wnt pathway is complex and multifunctional and that the manipulation of Dkk-1 might have multiple effects besides the possible treatment of insulin resistance.

Applicant argues that, "Indeed, the art would discloses that downregulation of Dkk-1 may be useful in cancer therapies" and cites several references.

Given the references cited above, clearly establishing the involvement of Dkk-1 and Wnt in some cancers, Applicant's arguments only strengthen the Examiner's position that the manipulation of Dkk-1 must be considered to be highly unpredictable.

Applicant again cites an article in *Reuters Health* quoting Dr. John Shaughnessy discussing his own work. Applicant argues that "one of ordinary skill could consider Dkk-1 antagonists useful" and that "one of ordinary skill at the time of the present invention believed it would be useful to develop Dkk-1 antagonists for purposes of treating human patients".

As set forth previously, the research does not involve treating insulin resistance nor repairing muscle, and the article also makes clear that the inhibition of Dkk-1 has not risen to the level of invention but is merely still an idea, "The researchers are currently [2003] in the early phases of developing and testing several compounds aimed at disabling Dkk-1". And while Dkk-1 antagonists may indeed someday prove "useful to develop" (as argued by Applicant), such is not the definition of an invention.

As set forth in the oft-quoted *Brenner v. Manson*, 383 U.S. 519,532 (1966), "But a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." Clearly, in this case, Applicant has failed to disclose an adequate conclusion, i.e., Applicant has failed to disclose that as of the priority date of the instant claims that antagonists of Dkk-1 could have been administered for the treatment of insulin resistance, or as a method of repairing or regenerating muscle, without undue experimentation.

5. No claim is allowed.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by

telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

7. **Please Note**: Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197.

12/2/08

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